Schwarz, Roderich E.

“Targeting TGFbeta in Pancreatic Cancer”

[We plan to test a new and unique approach to treatment of pancreatic cancer by blocking the receptor activity of TGFß, which in several different ways helps the cancer cells to grow.]

Pancreatic cancer is the fourth-leading cause of cancer death for both men and women, and only 4% of people affected with it do survive 5 years. Pancreatic cancers have a high rate of genetic changes that affect the function of transforming growth factor beta (TGFß); TGFß is the main downregulator of cell growth in gland-like or duct-lining cells, from which pancreatic cancer cells are derived. The majority of these cancer cells lack one or more proteins which mediate the TGFß signal within the cell, so that its break-like effect on cell growth is lost. In addition, more than half of pancreatic cancer cells produce abnormal amounts of TGFß, which provides the cancerous cell with a growth advantage. This growth advantage due to self-made TGFß has two components: a direct effect on the cancer cell, since the brake is lost (called autocrine effect), and an effect on surrounding cells that then helps the cancer cell grow (termed paracrine effect). Paracrine TGFß effects include changes on attachment forces between cells (making them more mobile and allowing the cancer cells to into healthy tissues), increased blood vessel growth, and a decrease in cancer-fighting immune cell activity. When TGFß exerts these effects, it does so by signaling through receptors that are present on most cells. We are proposing to work with novel drugs that are designed to block the signaling function of these receptors. Cultured human pancreatic cancer cells will be tested in the laboratory for the effect that TGFß receptor-blocking agents have, such as cell growth, cell attachment molecules, ability of cells to move in a culture dish, and the effect on the cells’ production of substances that stimulate the growth of blood vessels. We then propose to test the TGFß receptor blockers in animal models of pancreatic cancer, and measure their effect on blood vessel formation within tumors. We have developed an animal model of pancreatic cancer that resembles the course of the human disease; in this model, too, TGFß receptor blockers will be tested. Finally, we plan to analyze tumor tissue samples obtained from cancer patients for the abnormalities found in TGFß production and TGFß signaling proteins, to see how many patients would benefit from possible treatment with these exciting drugs. The new aspects of such treatment are that such drugs would not only work on cancer cells directly, but also work on surrounding cells which are primed to help the cancer cells grow. We expect that the impact of this double therapy approach will lead to new and important treatment strategies with special relevance to this most deadly cancer of all, pancreatic cancer.